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TITLE: Angiotensin IV peptides and receptor

Detailed Description Text (57):

In another embodiment of the invention, antagonists of AIV are provided that bind to the AT4 receptor. Presently particularly preferred antagonists of the invention include the non-peptide divalinal AIV and the C-terminal substituted tripeptide NleY1 amide, as described in Example 4, although other antagonists will be readily apparent from the data and disclosure set forth herein.

Detailed Description Text (72):

As shown in the examples AIV is active in endothelial cells in enhancing cellular proliferation (as evidenced by thymidine incorporation) and stimulating production of endothelial cell relaxing factor (EDRF). These results also show the non-interaction of G-proteins with vascular AT4 receptors in bovine aortic or coronary venous endothelial cells. The results set forth in the Examples further identify a role for the AIV ligand-AT4 receptor interactions in triggering normal and/or hyperplastic growth of endothelial cells in sites of tumors or traumatic or wound injury, and angiogenesis, and a therapeutic use for AIV analogs, agonists, antagonists, and derivatives and covalently modified AIV peptide ligands that are capable of inhibiting vascular smooth muscle cell growth in such hyperplastic states while at the same time promoting endothelial cell growth. The agonist compositions are also useful for encouraging endothelial cell growth, e.g., in wound sites; antagonists for discouraging vascularization in tumor sites. In addition, the AT4 receptor-ligand system may play a role in triggering vasodilation through a selective effect on subpopulations of endothelial cells that exist in particular vascular beds (e.g., in the heart, lung, liver, kidney, brain and the like). As shown in the examples, increased renal blood flow occurs in rats following infusion of AIV ligands and taken together with the demonstrated ability of AIV to stimulate EDRF production in vascular endothelial cells, the AIV ligand-receptor system mediates actions of angiotensin that fall within the bounds of cardiovascular regulation and body water homeostasis. Thus, therapeutic uses for AIV analogs, AIV agonists and antagonists, and derivatives and covalently modified AIV peptide ligands include promoting renal blood flow (e.g., in chronic kidney diseases) or, alternatively, inhibiting renal blood flow (i.e., using inhibitors and antagonists of AIV), e.g., in conditions of hyperacute renal dysfunction and water loss, or during renal surgical procedures.

Detailed Description Text (106):

As further shown in Table 7, the D-substitution and glycine-substitution data confirms that positions 1-3 of the AIV molecule are critical for determining binding affinity to the receptor. Positions 4-6 are less critical. In fact removal of C-terminal groups appears to enhance binding affinity perhaps by reducing steric constraints. Ligands containing C-N nonpeptide bonds can be produced that possess high affinity. In general, highest affinity is obtainable by dual modifications at bonds between amino acids 1-2 and 3-4. Val(1)Val(3) AIV appears totally resistant to enzymatic degradation upon exposure to rat kidney homogenates. As further shown in Table 7, tripeptides containing straight chain aliphatic amino acids in position 1 exhibit high affinity. To date, the highest affinity is achievable with the Nle-Y-I amide, suggesting that amides are preferable to free acids and that the chain length found in Nle is optimal (both longer and shorter bind with lower affinity).

Detailed Description Text (123):

In endothelial cells (such as bovine coronary venular endothelial cells), it has been reported previously that these cells may play a critical role in angiogenesis (review, 21). In one study by others angiotensins were reported to be capable of stimulating angiogenesis (22). However, studies in the inventors' laboratory over the past ten years have failed no less than six times to demonstrate detectable levels of AII receptors in preparations of endothelial cells that were free of smooth muscle contamination (a finding contradictory to one report that AII receptors may be present on endothelial cells, (23). In addition, AII and Sar.sub.1,Ile.sub.8 -AII have been reported to stimulate bovine endothelial cell proliferation (24), but the possible mechanisms were not clear, especially in light of other studies reportedly showing that AII and Sar.sub.1,Ile.sub.8 -AII were rapidly metabolized in tissues and biological fluids to smaller metabolites. In light of the present disclosure it is now clear, in hindsight, that hydrolysis of AII or AIII to AIV can result in binding of AIV to AT4 receptors on endothelial cells with triggering of cell proliferation, and may possibly be involved in the initiation of hyperplastic growth of endothelial cells or vascular smooth muscle cells.

Detailed Description Text (294):

Given the presence of AT4 receptors in the brain (Example 2, above; FIGS. 6-10) and most likely in cognitive and motor memory and learning centers (i.e., hippocampus, frontal cortex, cerebellum, and thalamus), and in areas within the hindbrain cardiovascular nuclei involving the tractus solitarius, it is reasonable to suspect that at least in some tissues AIV ligand is produced locally in neural tissues, i.e., by synthesis of AI and conversion to AIV. Two scenarios of local production can be envisioned. In the first, AIV ligand is produced locally from precursors synthesized in the tissue. In the second, circulating AIV precursors (e.g., AI, AII or AIII) are converted locally to AIV ligand. Whether the first or second scenario is an operative mechanism in a particular tissue can be determined by introducing radiolabeled precursors (i.e., ¹²⁵I-AI) into the bodily fluid bathing the tissue (e.g., plasma or CNS fluid), and by then collecting samples of the fluid at different times and assaying by reverse-phase HPLC to determine if the AIV precursor has been converted to AIV ligand in the fluid. If it has been converted, the second scenario is operative; if it has not been converted a second series of experiments is conducted. In the second series of experiments biosynthesis of AIV precursors is evaluated (i.e., with radiolabeled amino acids) and conversion of the precursor into AIV ligand is examined in pulse-chase type experiments. If biosynthetically radiolabeled AIV precursor chases into AIV ligand, then the first scenario is operative in the tissue.

Other Reference Publication (7):

Harding, J.W. et al., "Angiotensin-Sensitive Neurons in the Rat Paraventricular Nucleus: Relative Potencies of Angiotensin II and Angiotensin III," Brain Res. 410:130-134 (1987).